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     (FILE 'HOME' ENTERED AT 08:54:14 ON 08 MAY 2002)

     INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,
     BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO,
CABA,
     CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB,
     DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...' ENTERED AT 08:54:26 ON
     08 MAY 2002
               SEA GDP-MANNOSE
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              48   FILE AGRICOLA
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     FILE 'CAPLUS, BIOSIS, MEDLINE, EMBASE, SCISEARCH, BIOTECHNO' ENTERED AT
     08:56:22 ON 08 MAY 2002
L2          1874 S L1 AND (SYNTHESI? OR BIOSYNTHESI OR PRODUC? OR MANUFACTUR?)
L3            96 S L2 AND (HYBRID OR CHIMER? OR FUSION OR DUAL-FUNCTION)
L4            32 DUP REM L3 (64 DUPLICATES REMOVED)
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4 ANSWER 16 OF 32 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 6
ACCESSION NUMBER: 1999:37915 CAPLUS
DOCUMENT NUMBER: 130:193578
TITLE: GDP-fucose synthetase from Escherichia coli: structure of a unique member of the short-chain dehydrogenase/reductase family that catalyzes two distinct reactions at the same active site
AUTHOR(S): Somers, William S.; Stahl, Mark L.; Sullivan, Francis X.
CORPORATE SOURCE: Small Molecule Drug Discovery, Genetics Institute, Inc., Cambridge, MA, 02140, USA
SOURCE: Structure (London) (1998), 6(12), 1601-1612
CODEN: STRUE6; ISSN: 0969-2126
PUBLISHER: Current Biology Publications
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In all species examd., GDP-fucose is **synthesized** from **GDP-mannose** in a 3-step reaction catalyzed by 2 enzymes, **GDP-mannose** 4,6-dehydratase and a **dual function** 3,5-epimerase-4-reductase named GDP-fucose synthetase (I). In this latter aspect, fucose **biosynthesis** differs from that of other deoxy and dideoxy sugars, in which the epimerase and reductase activities are present as sep. enzymes. Defects in GDP-fucose **biosynthesis** have been shown to affect nodulation in bacteria, stem development in plants, and are assocd. with the immune defect leukocyte adhesion deficiency type II in humans. Here, the authors detd. the structure of I from E. coli at 2.2 .ANG. resoln. The structure of I was found to be closely related to that of UDP-galactose 4-epimerase, and more distantly to other members of the short-chain dehydrogenase/reductase family. The authors also detd. the structures of binary complexes of I with its substrate, NADPH, and its **product**, NADP. The nicotinamide cofactors bound in the syn and anti conformations, resp. I bound its substrate, NADPH, in the proper orientation (syn) for transferring the 4-pro-S hydride of the nicotinamide. The authors obsd. a single binding site in I for the second substrate, GDP-4-keto-6-deoxy-mannose. This implies that both the epimerization and redn. reactions occur at the same site in the enzyme. As is the case for all members of the short-chain family of dehydrogenase/reductases, I retained the Ser-Tyr-Lys catalytic triad. It is proposed that this catalytic triad functions in a mechanistically equiv. manner in both the epimerization and redn. reactions. Addnl., the x-ray structure allowed the authors to identify other residues that were potentially required for substrate binding and catalysis.

L4 ANSWER 15 OF 32 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:226493 BIOSIS
DOCUMENT NUMBER: PREV199800226493
TITLE: Molecular cloning of human **GDP-mannose** 4,6-dehydratase and reconstitution of GDP-fucose **biosynthesis** in vitro.
AUTHOR(S): Sullivan, Francis X. (1); Kumar, Ravindra; Kriz, Ronald; Stahl, Mark; Xu, Guang-Yi; Rouse, Jason; Chang, Xiao-Jia; Boodhoo, Amechand; Potvin, Barry; Cumming, Dale A.
CORPORATE SOURCE: (1) Small Mol. Drug Discovery, Genet. Inst. Inc., 87 Cambridgepark Dr., Cambridge, MA 02140 USA
SOURCE: Journal of Biological Chemistry, (April 3, 1998) Vol. 273, No. 14, pp. 8193-8202.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
AB We have cloned the cDNA encoding human **GDP-mannose** 4,6-dehydratase, the first enzyme in the pathway converting **GDP-mannose** to GDP-fucose. The message is expressed in all tissues and cell lines examined, and the cDNA complements Lec13, a Chinese Hamster Ovary cell line deficient in **GDP-mannose** 4,6-dehydratase activity. The human **GDP-mannose** 4,6-dehydratase polypeptide shares 61% identity with the enzyme from Escherichia coli, suggesting broad evolutionary conservation. Purified recombinant enzyme utilizes NADP+ as a cofactor and, like its E. coli counterpart, is inhibited by GDP-fucose, suggesting that this aspect of regulation is also conserved. We have isolated the **product** of the dehydratase reaction, GDP-4-keto-6-deoxymannose, and confirmed its structure by electrospray ionization-mass spectrometry and high field NMR.

Using purified recombinant human **GDP-mannose** 4,6-dehydratase and FX protein (GDP-keto-6-deoxymannose 3,5-epimerase, 4-reductase), we show that the two proteins alone are sufficient to convert **GDP-mannose** to GDP-fucose in vitro. This unequivocally demonstrates that the epimerase and reductase activities are on a single polypeptide. Finally, we show that the two homologous enzymes from E. coli are sufficient to carry out the same enzymatic pathway in